IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No.:	**DC-0156**
Inventors:	**DeLeo and Weinstein**
Serial No.:	**09/857,385**
Filing Date:	**July 6, 2001**
Examiner:	**Donna A. Jagoe**
Customer No.:	**26259**
Group Art Unit:	**1614**
Confirmation No.:	**4729**
Title:	**An Animal Model and Compounds Identified via this Model for Treatment of Chronic Pain**

Electronically Submitted via EFS-Web
Date: **August 7, 2008**

I hereby certify that this paper is being electronically submitted on the date indicated above to the Commissioner for Patents, U.S. Patent & Trademark Office (AF).

By _____
Typed Name: **Jane Massey Licata, Reg. No. 32,257**

Commissioner for Patents
U.S. Patent & Trademark Office
(AF)

APPEAL BRIEF

TABLE OF CONTENTS

I. Real Party in Interest

The real party in interest is Trustees of Dartmouth College.

II. Related Appeals and Interferences

There are no related appeals or interferences.

III. Status of Claims

Claim 1 is pending in this application.

Claims 2-7 have been canceled.

Claim 1 has been rejected and is on appeal. A claims appendix including the text of the appealed claim is attached.

IV. Status of Amendments

The claim amendments filed March 5, 2003; September 19, 2003; December 21, 2004; July 6, 2005; May 11, 2006; October 27, 2006; January 24, 2007; September, 19, 2007; and October 23, 2007 were entered. The rejections to claim 1 were maintained in the Advisory Action dated June 6, 2008.

V. Summary of the Claimed Subject Matter

Claim 1 defines a method of reducing lower back pain with radiculopathy in an animal with such pain consisting of administering methotrexate to the animal so that lower back pain with radiculopathy is reduced. See page 4, lines 13-17. The method of the invention involves administration of the drug locally into the spinal cord but not the brain, by intrathecal administration. See page 5, lines 27-33. The method of the present invention also stipulates that methotrexate is administered intrathecally at a dose level of 1 mg/kg. See page 8, lines 14-15, and page 9, lines 22-25.

VI. Grounds of Rejection to be Reviewed on Appeal

Whether claim 1 should stand rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

Whether claim 1 should stand rejected under 35 U.S.C. §103(a) as being unpatentable over Chamberlain et al. (1998) and Biomethodology of the Rat (http://research.uiowa.edu/animal/print.php?.

VII. Arguments

A. The Rejection of Claim 1 Under 35 U.S.C. §112, First Paragraph Should Be Withdrawn

The Examiner has suggested that the claim contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner suggests that the term "into the spinal cord but not the brain" is a concept that was not present in the specification as originally filed and that any negative limitation or exclusionary proviso must have basis in the original disclosure. Appellants respectfully disagree.

As discussed in the Reply to the Final Rejection dated April 24, 2008, the Reply to the Interview Summary dated October 16, 2007, and explained in detail in the Office Action response filed September 19, 2007, the basis for the amended claim 1 language "intrathecally into the spinal cord but not into the brain" is the knowledge of one of skill at the time the application was filed and as such is not required to be explicitly taught in the specification as filed. MPEP 2163 states "What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail." (Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d at 1384, 231 USPQ at 94). Further MPEP 2163 states that "If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate written description requirement is met." (Vas-Cath, 935 F.2d at 1563, 19 USPQ2d at 1116; Martin v. Johnson, 454 F.2d 746, 751, 172 USPQ 391, 395 (CCPA 1972)). Therefore, contrary to the Examiner's assertion, there is no need to incorporate by reference the text of the Human Anatomy and Physiology text relied on by the Appellants because teachings of

that text would have been known to one of skill in the art. Appellants have relied on support found in the general principles of physiology and anatomy that were known at the time the application was filed. As a result, claim 1 meets the requirements of 35 U.S.C. 112, first paragraph.

Apparently, the Examiner has failed to consider that one of ordinary skill in the art would have the understanding of the difference of intrathecal versus intraventricular administration wherein intrathecal administration would, by definition, result in injection of drug "into the spinal cord but not into brain". Appellants would also point out that this fact was acknowledged in a telephone interview held on October 2, 2007, and at that time it was even indicated that the claim was allowable since this was textbook knowledge.

In the Advisory Action dated June 6, 2008, the Examiner points to teaching in the same textbook that "circulation of the cerebrospinal fluid through the brain ventricles is designed such that only a very small amount of the CSF from the ventricles circulates into the central canal of the spinal cord". The Examiner then states that this proves that a small dose of methotrexate administered intrathecally would circulate into the brain. However, Appellants respectfully submit that even if a small amount of a dose of methotrexate would reach the brain, the textbook clearly teaches that intraventricular administration of a drug is administration into the brain itself while intrathecal administration is administration not into the brain but into the spinal cord. The two compartments of CSF are separate compartments and thus are separate compartments for drug administration as well. Appellants believe it is common knowledge that the two routes of administration of a drug are different as they target different tissues, spinal cord (intrathecal) as compared to the brain (intraventricular).

Accordingly, Appellants believe that claim 1 meets the

requirements of 35 U.S.C. 112, first paragraph based on the knowledge of one of skill in the art at the time the application was filed, as evidenced by teachings found in textbooks available to one of skill at the time the application was filed.

B. The Rejection of Claim 1 Under 35 U.S.C. §103(a) as Being Unpatentable Over Chamberlain et al. (1998) and *Biomethodology of the Rat* (http://research.uiowa.edu/animal/print.php? Should Be Withdrawn

The Examiner has suggested that Chamberlain et al. (1998) teach intraventricular administration of methotrexate at a dose of 2 mg daily (40 mg total dose) to patients with leptomenigeal metastases presenting with radiculopathy, and that the method of administering intrathecally would overlap with this method. Further, the Examiner suggests that the reference on *Biomethodology of the Rat* teaches that a rat weighs about 250 g and thus the 1 mg/kg dose of the present invention would equate to about 0.8 mg given to a rat. Therefore, the Examiner suggests these references teach the limitations of claim 1. Further, the Examiner suggests that it is routine to "dramatically vary dosage to obtain data on parameters such as toxicity" and thus it would have been obvious to use methotrexate in a dose of 1 mg/kg. In the Advisory Action dated June 6, 2008, the Examiner states she stands behind her dose calculation and further suggests that methotrexate should not be given in daily doses, is toxic, and that a dose of 1 mg/kg in an 80 kg human would be toxic unless leucovorin rescue was performed. The Examiner supports these statements by referring to a reference only as "Jones et al.", without providing the reference or any further citation. As discussed in detail in the previous responses and during a telephone interview, Appellants respectfully disagree with the Examiner's conclusions regarding the cited references.

First, Appellants respectfully remind the Examiner that the issue of dose and the discussions in previous replies and during a

telephone interview have been directed to the Examiner's position that dose extrapolation from mg/kg body weight, as taught in the specification as filed and as claimed, can be extrapolated to doses in mg (the metric taught by Chamberlain et al.) without considering body weight of the species. Accordingly, it is in this exercise that Appellant believes the Examiner has made several errors not only in statements about doses but also in reasoning regarding basic principles of pharmacology and dose selection for drugs used to treat pain. First, in order to compare the teachings of Chamberlain et al. (1998) with the teachings of the specification as filed, it is necessary to extrapolate from the dose of 2 mg in a human that is taught explicitly by Chamberlain et al. (1998), as well as to compare the extrapolated dose with the dose of the instant claim which is 1 mg/kg in a rat.

It is a general principle of pharmacology that if an effective dose is taught to be a dose in mg/kg body weight, then in order to extrapolate the dosing from a rat, the species taught in the specification as filed, to a dose that might be used in humans, the species of the Chamberlain et al. reference, the dose extrapolation would be done based on consideration of the difference in body weights, not by ignoring the body weight differences as has been suggested by the Examiner. The contrary is also true. One of skill in the art would never extrapolate from a mg dose in humans to a mg dose in rats without first correcting the mg dose for body weight in humans. This is because of the large difference in size of a human versus a rat. If 2 mg is safe in a very large species (man), that dose could be lethal to a rat, a much smaller species. Instead, dosing would be done by first correcting for body weight. In other words, a 2 mg dose in humans would be 2 mg divided by 60-70 kg body weight which is 0.029 to 0.033 mg/kg/day, a dose much lower than 1 mg/kg as now claimed. The reverse is also true. One of skill would never take a 1 mg/kg dose in a rat and assume that that dose in mg, about 0.25 mg in the rat based on 250 grams of body

weight, would have efficacy in a human based on the large difference in body size of the human as compared to the rat. The Examiner is totally mistaken in suggesting that one of skill in the art would ignore well-established principles of dose extrapolation and ignore the differences in body size when extrapolating from a rat to humans or even the reverse extrapolating from humans down to rats (as the Examiner is doing in the instant case). If Chamberlain is teaching use of 2 mg per day in a human, that is NOT simply 2 mg in a rat. This is because of the level of toxicity that would be expected in giving the same dose to a rat as is used in a human. Rats would be receiving a dose that was much too high based on the size of the animal (200 to 800 grams for a rat versus 60 to 70 kg for humans). As a result, Appellants believe that one of skill would not understand or assume that the dosage taught by Chamberlain, a much lower dose of 0.029 to 0.033 mg/kg/day, would make obvious use of a much higher dose, 1 mg/kg. This is because of the issue of considering whether the higher dose is effective as well as safe. Nowhere does the reference of Chamberlain et al. teach or suggest use of a dose in the range taught and successfully used in the specification as filed.

In addition, the Examiner asserts that methotrexate is a toxic medication and that it is not administered on a mg/kg basis because of the risk of toxicity, including death. Appellants respectfully disagree. As discussed in the previous replies, methotrexate is administered for cancer treatment on the basis of body surface area not mg/kg because that is the dosage method that has been used in cancer treatment efficacy studies. It was a method developed for cancer clinical trial design decades ago and as discussed in a paper in the published literature in 1998, the use of the body surface area instead of body weight for dosing was merely to assist in design of phase I clinical studies for anticancer agents (see Ratain, M.J. 1998. *J. Clin. Oncol.* 16:2297-2298). In the 1998 paper, the physician states that the use of body surface area is

not science-based and related strictly to anything such as toxicity potential but has become instead myth handed down through generations. Although the author of the paper does not specifically focus on methotrexate, the paper is directly relevant to methotrexate because indeed its efficacy studies for cancer were performed using dosing on a surface area basis rather than body weight. Contrary to the Examiner's suggestion, the use of mg/kg for methotrexate is not inappropriate for pain treatment as claimed. Although use of body surface area dosing is routine in oncology it is NOT ROUTINE in pain therapy. In fact, the teaching of the specification as filed shows that a low dose of methotrexate has efficacy to treat pain when it is given intrathecally into the spinal cord. It must be remembered that one of skill would understand the toxicity profile of methotrexate, which is well-known in the art, and as such would monitor patients for the onset of toxicity and the need to adjust dosing schedules depending on responses. Moreover, Appellants respectfully point out that at page 8, lines 14-35, the specification as filed discusses the issue of toxicity and describes the dose of 1 mg/kg as being one quarter of the maximally tolerated dose in rats, the animals treated in the instant invention. Also, Appellants point out that the dosing of the method of the present invention involves a single dose of methotrexate and not daily dosing with a 1 mg/kg dose, wherein use of the single dose was capable of treating chronic pain. At most, the specification as filed teaches use of 2 doses of 1 mg/kg. With these dosing regimens, the specification as filed specifically teaches that there was no significant toxicity seen in the animals.

With the teaching provided by the specification as filed, one of skill would understand that dosing with methotrexate at 1 mg/kg intrathecally is not directly comparable to intravenous or oral dosing with the same dose level. In fact, it is only speculation by the Examiner that the dosing regimen of the instant invention would involve need for leucovorin rescue. This is because the issues

raised by the Examiner in the Advisory Action dated June 6, 2008 are directed to discussion of the potential toxicity of an oral or an intravenous dose of methotrexate, where 1 mg/kg, which would be an 80 mg dose in a 80 kg human, is a dose that could potentially produce toxicity. It should also be noted that the reference cited by the Examiner in the Advisory Action (Jones et al.) was not provided nor specifically described by the Examiner in a way that Appellants could more carefully judge the validity of the Examiner's statements. Regardless, however, oral and intravenous dosing with methotrexate are not part of the present invention which is limited to intrathecal administration of the drug or administration of the drug directly into the spinal cord but not the brain.

Therefore, as discussed in the previous replies, although it is true that methotrexate is often dosed on a mg/m^2 basis in cancer therapy, this is NOT the case for drugs used to treat pain. This is because, as taught only in the specification as filed, one of skill would need to understand how efficacy related to safety in any particular species. That is why the teaching of the specification as filed is clear in defining dose on a mg/kg basis, to allow one of skill to understand how to extrapolate doses across different species. Chamberlain et al., however, is silent on this issue and thus would not be used by one of skill to extrapolate from a 2 mg dose in humans, which they would understand to be a dose of approximately 0.029 mg/kg/day based on a 70 kg individual or 0.033 mg/kg/day based on a 60 kg individual, to a dose in a smaller animal such as a rat. The 2 mg dose of Chamberlain et al. is much lower than the dose range claimed in the instant invention and as such would not be obvious to one of skill in the art. Again as well, it must be remembered that it is a general principle of pharmacology that you extrapolate doses across species based on mg/kg not mg alone and not on mg/m^2 for pain treatment.

Under 35 U.S.C. §103, the factual inquiry into obviousness

requires a determination of: (1) the scope and content of the prior art; (2) the differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) secondary considerations. *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966). The Court quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006), stated that "'[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.'" *KSR*, 550 U.S. at ___, 82 USPQ2d at 1396. See also MPEP 2141.

In the instant case, not only does the cited reference fail to teach or suggest the invention as claimed, the rationale behind the Examiner's conclusion of obviousness is simply flawed. Indeed, the cited reference teaches use of methotrexate to treat cancer NOT lower back pain with radiculopathy. Moreover, the paper teaches use of a much lower dose range and a different route of administration. Therefore, this reference fails to teach the limitations of the claim as amended and also fails to provide one of skill with any guidance for successfully carrying out the method as claimed. It is only with the specification in hand that one of skill would understand that intrathecal administration at a dose level of 1 mg/kg body weight would be effective and safe for treating lower back pain with radiculopathy. Accordingly, this reference cannot make obvious the invention of the amended claim.

Reversal of the Examiner's rejections of claim 1 is therefore respectfully requested.

Respectfully submitted,

Jane Massey Licata
Registration No. 32,257

Date: **August 7, 2008**

Licata & Tyrrell P.C.
66 E. Main Street
Marlton, NJ 08053

856-810-1515

VIII. Claims Appendix

Claim 1 (previously presented): A method of reducing lower back pain with radiculopathy in an animal having lower back pain with radiculopathy consisting of locally administering methotrexate intrathecally into the spinal cord but not the brain of said animal at a dose level of 1 mg/kg, so that lower back pain with radiculopathy is reduced.

IX. Evidence Appendix

Appendix A. Human Anatomy and Physiology, 2nd Edition, Elaine N. Marieb (ed)., Benjamin/Cummings Publishing Company: Redwood City, CA, pages 404-405.

Appendix B. Ratain, M.J. 1998. *J. Clin. Oncol.* 16:2297-2298.

Human Anatomy and Physiology

SECOND EDITION

Elaine N. Marieb, R.N., Ph.D.
Holyoke Community College

The Benjamin/Cummings Publishing Company, Inc.

Redwood City, California • Menlo Park, California
Reading, Massachusetts • New York • Don Mills, Ontario
Wokingham, U.K. • Amsterdam • Bonn • Sydney
Singapore • Tokyo • Madrid • San Juan

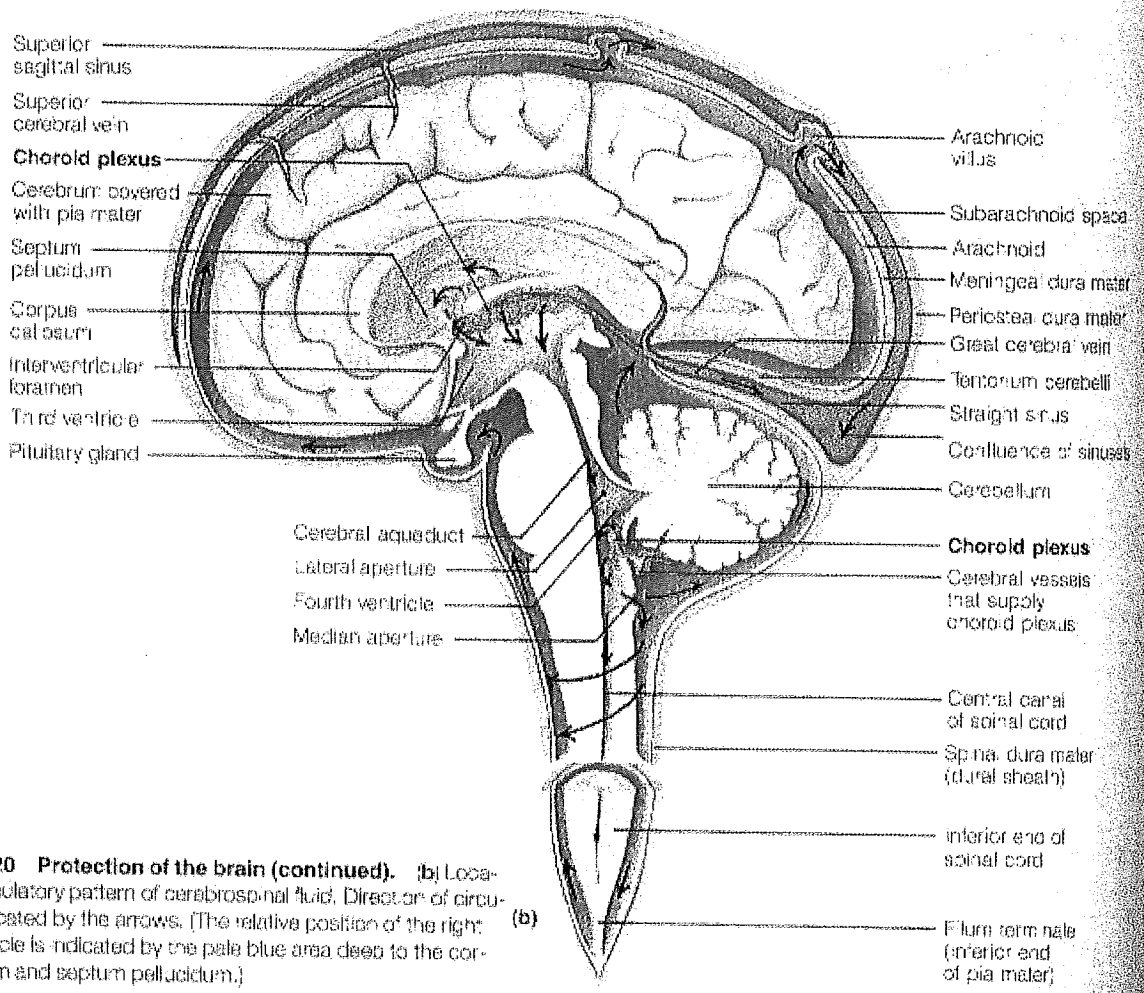

Figure 12.20 Protection of the brain (continued). (b) Location and circulatory pattern of cerebrospinal fluid. Direction of circulation is indicated by the arrows. (The relative position of the right lateral ventricle is indicated by the pale blue area deep to the corpus callosum and septum pellucidum.)

Cerebrospinal Fluid

Cerebrospinal fluid (CSF), found in and around the brain and spinal cord, forms a liquid cushion that gives buoyancy to the CNS organs. By floating the jellylike brain, the CSF effectively reduces brain weight by 97% and prevents the brain from crushing under its own weight. CSF also protects the brain and spinal cord from blows and other trauma. Additionally, although the brain has a rich blood supply, cerebrospinal fluid helps to nourish the brain.

CSF is a watery "broth" similar in composition to blood plasma, from which it arises. However, it contains less protein and more vitamin C, and its ion concentration is different. For example, CSF contains more sodium, chloride, magnesium, and hydrogen ions than blood plasma, and fewer calcium and potassium ions. CSF composition, particularly its pH, is important in the control of cerebral blood flow and breathing, as described in later chapters. CSF also transports hormones along the ventricular channels.

The **choroid plexuses** that hang from the roof of each ventricle (Figure 12.20b) form CSF. These plexuses are frond-shaped clusters of capillaries (*plexus* = interwoven) enclosed by ciliated epithelial cells that are continuous with the ependymal cells lining the ventricles. Although the capillaries of the choroid plexuses are fairly permeable and tissue fluid filters continuously from the bloodstream, the choroid plexus epithelial cells are joined by tight junctions and have ion pumps that allow them to modify this filtrate by actively transporting only certain ions across their membranes into the CSF pool. This sets up ionic gradients that cause water to diffuse into the ventricles as well. In adults, the total CSF volume of about 150 ml (about half a cup) is replaced every 3 to 4 hours, hence 900–1200 ml of CSF are formed daily. The choroid plexuses also help to cleanse the CSF by removing waste products and other unnecessary solutes.

Once produced, CSF moves freely through the ventricles. Some CSF circulates from the ventricles into the central canal of the spinal cord, but most enters the subarachnoid space via the lateral and medial apertures in the walls of the fourth ventricle.

(Figure 12.20b). The constant motion of the CSF is aided by the cilia of the ependymal cells lining the ventricles. In the subarachnoid space, CSF bathes the outer surfaces of the brain and cord and then returns to the blood in the dural sinuses via the arachnoid villi.

Ordinarily, CSF is produced and drained at a constant rate. However, if something (such as a tumor) obstructs its circulation and/or drainage, it begins to accumulate and exert pressure on the brain. This condition is called *hydrocephalus* ("water on the brain"). Hydrocephalus in a newborn baby causes its head to enlarge; this is possible because the skull bones have not yet fused. In adults, however, hydrocephalus is more likely to result in brain damage because the skull is rigid and hard, and accumulating fluid compresses the blood vessels serving the brain and crushes the soft nervous tissue. Hydrocephalus is treated by inserting a shunt in the ventricles that drains off the excess fluid into a vein in the neck. ■

Blood-Brain Barrier

The **blood-brain barrier** is a protective mechanism that helps ensure that the brain's environment remains stable. No other body tissue is so absolutely dependent on a constant internal milieu as is the brain. In other body regions, the extracellular concentrations of hormones, amino acids, and ions are in constant flux, particularly after eating or exercise. If the brain were exposed to such chemical variations, the neurons would fire uncontrollably, because some hormones and amino acids serve as neurotransmitters and certain ions (particularly potassium) modify the threshold for neuronal firing.

Blood-borne substances within the brain's capillaries are separated from the extracellular space and neurons by (1) the continuous endothelium of the capillary wall; (2) a relatively thick basal lamina surrounding the external face of the capillary; and to a limited extent (3) the bulbous "feet" of the astrocytes that cling to the capillaries. The capillary endothelial cells are almost "seamlessly" joined all around by *tight junctions* (see Chapter 20, p. 636), making them the least permeable capillaries in the entire body. This relative impermeability of brain capillaries constitutes most (if not all) of the blood-brain barrier. Although it was formerly assumed that the astrocytes contribute to the blood-brain barrier, the electron microscope has revealed that their end feet are too far apart to form any true seal. It now appears that the major role of the astrocyte end feet is to provide the signals that stimulate the endothelial cells of the brain capillaries to form the tight junctions characteristic of the blood-brain barrier.

The blood-brain barrier is a selective, rather than an absolute, barrier. Nutrients, such as glucose, essential amino acids, and some electrolytes, move passively by facilitated diffusion through the endothelial cell membranes. Blood-borne metabolic wastes, such as urea and creatinine, as well as proteins, certain toxins, and most drugs, are prevented from entering brain tissue. Small nonessential amino acids and potassium ions not only are prevented from entering the brain, but also are actively pumped from the brain across the capillary endothelium.

The barrier is ineffective against fats, fatty acids, oxygen and carbon dioxide, and other fat-soluble molecules that diffuse easily through all plasma membranes. This explains why blood-borne alcohol, nicotine, and anesthetics can affect the brain.

The structure of the blood-brain barrier is not completely uniform. As noted above, the capillaries of the choroid plexuses are very porous, but the epithelial cells surrounding them have tight junctions. In some brain areas, the blood-brain barrier is entirely absent and, in such areas, the capillary endothelium is quite permeable, allowing blood-borne molecules easy access to the neural tissue. One such region is the vomiting center of the brain stem, which monitors the blood for poisonous substances. Another is in the hypothalamus, which regulates water balance, body temperature, and many metabolic activities; lack of a blood-brain barrier here is essential to allow the hypothalamus to sample the chemical composition of the blood. The blood-brain barrier is incompletely developed in newborn and premature infants, and potentially toxic substances can readily enter the CNS and cause problems not seen in adults.

Injury to the brain, whatever the cause, may cause a localized breakdown of the blood-brain barrier. Most likely, this reflects some change in the capillary endothelial cells or their tight junctions. This supposition is borne out by a new procedure that infuses a concentrated solution of mannitol (sugar) prior to infusing chemotherapeutic drugs. The mannitol causes the capillary endothelial cells to shrink, opening up gaps between their tight junctions that allow the drugs to breach the blood-brain barrier and gain access to brain tumors. ■

Homeostatic Imbalances of the Brain

Brain dysfunctions are unbelievably varied and extensive. We have mentioned some of them already, and we will discuss developmental problems in the final section of the chapter. Here, we will focus on traumatic brain injuries and degenerative disorders.

Traumatic Brain Injuries

Head injuries are the leading cause of accidental death in the USA. Consider, for example, what hap-

Reprinted from
Volume 16, Number 7 **July 1, 1998**

JOURNAL OF CLINICAL ONCOLOGY

Body-surface area as a basis for dosing of anticancer agents: science, myth, or habit?

MJ Ratain

EDITORIAL

Body-Surface Area as a Basis for Dosing of Anticancer Agents: Science, Myth, or Habit?

WHAT IS body-surface area (BSA), and what does it have to do with the dosing of anticancer agents? BSA rarely is measured, but rather estimated as a mathematical function of height and weight.[1,2] Freireich et al[3] first described the importance of BSA in allometric scaling, so that dosing in lower mammals, such as rodents, could be extrapolated to dosing in humans. The investigators' original goal was to define a safe starting dose for phase I trials of new anticancer agents.

How did we go from BSA-based dosing in phase I trials to BSA-based dosing of virtually all drugs prescribed by oncologists, including even some antiemetics? Phase I trials defined a maximum tolerated dose, normalized to BSA, that then was used in phase II trials, and eventually incorporated into the Food and Drug Administration-approved labeling. In addition, the initial users of BSA-based dosing then trained the next generation of oncologists, and so on, which created the myth that BSA-based dosing is required for safe and effective administration of cytotoxic chemotherapy.

Why have oncologists persisted in using BSA-based dosing for cancer chemotherapy? Because most chemotherapy drugs are quite toxic, precise calculation of doses of all drugs may provide physicians with the psychologic benefit of tailoring the dose to each individual patient. In contrast, the administration of the same dose to all patients might imply that the physician did not know the correct dose for the individual patient, and therefore, must prescribe the same dose to everybody, many of whom would have significant toxicity.

Does BSA-based dosing make pharmacologic sense? It is intuitive that measures of body size would be correlated to organ size and function, but is BSA, a function of height and weight, the best correlate? This question is not unique to oncology, and has been studied for a variety of drugs. The measure of body size that has been suggested to be the best correlate to clearance is lean body mass (LBM), which has been shown to be better than BSA or weight for multiple agents, including grepafloxacin, lithium, and remifentanil.[4-7] Most relevant to the article by Gurney et al[8] in this issue of the *Journal of Clinical Oncology* is another small study of epirubicin from Australia (10 patients), which concluded that LBM should be further evaluated and tested in dose optimization studies.[9]

Is dosing on the basis of BSA harmful? For some drugs, it clearly has been shown that there is no relationship between BSA and clearance.[10-12] In this case, the use of BSA-based dosing results in the administration of a standard dose multiplied by a random number—the ratio of the patient's BSA to an average BSA (1.73 m^2). Calculation of BSA-based doses, although routinely performed, still introduces a small, but real, risk of a major arithmetic error, with serious consequences. BSA-based dosing also increases pharmacy expenses, because it increases pharmacist time and results in drug wastage caused by partial use of single-dose vials. However, the most important repercussion of BSA-based dosing is the false sense of accuracy that results from the series of detailed calculations required to treat a patient (BSA-based dosing definitely is precise, but it certainly is not accurate). This may decrease the incentive to use other potential predictors of drug clearance, some of which currently are being commercialized, such as the erythromycin breath test (to predict CYP3A4 activity)[13] and genotyping for polymorphisms in drug-metabolizing enzymes.[14]

What should we do about the current situation? One might suggest that we should abandon BSA and switch to LBM-based dosing. Unfortunately, there is no standard method for determining LBM, which is correlated with height, weight, and age.[4,15,16] It is interesting that these are precisely the variables that are used to determine dosing in current practice, height and weight through their determination of BSA, and age, which often is factored into decisions that regard the aggressiveness of therapy. However, like BSA, LBM does not take into account other important factors that determine drug clearance, such as genetically determined polymorphisms in drug metabolizing activity and reduced drug clearance caused by the effect of the malignancy itself.

A better plan is to admit that we have very inaccurate dosing guidelines for our current drugs, and to develop new drugs differently. New phase I studies only should use BSA for allometric scaling purposes (estimation of the starting dose), and all dose levels should incorporate flat dosing, with all patients at a dose level receiving the same dose. At the completion of the study, BSA should be analyzed as a possible determinant of drug clearance, in the same way that one currently analyzes factors such as age, gender, and renal function. It also would be important to treat an adequate number of patients at the recommended phase II dose to evaluate possible relationships between BSA (and other factors) and toxicity. It particularly is important to consider these issues as oral drug therapy permeates oncology practice,[17] because it will be important to keep oral dosing regimens as simple as possible, without resorting to patients counting out one 25 mg and three 1 mg pills. Individualized dosing of oral anticancer drugs eventually may incorporate

evaluation of pretreatment predictors of clearance (as currently is used for carboplatin), or the monitoring of plasma concentrations if clinical benefit can be shown.[18]

What should we do with regard to currently marketed drugs? It is critical to begin to explore the feasibility of simplifying regimens, as exemplified by the study of epirubicin by Gurney et al[8] in this issue. Although this only is a small study with limited power to determine if a significant relationship exists between BSA and epirubicin pharmacokinetics or toxicity, it clearly shows the feasibility of simplifying dosing. A similar study by the Cancer and Leukemia Group B is in progress which evaluates a fixed dose of paclitaxel (360 mg) in women. It also would be reasonable to eliminate BSA-based dosing for all drugs for which there is clear historic evidence of a lack of relationship of BSA and clearance. As an example, one could replace etoposide doses of 100 mg/m^2 with fixed doses of 175 mg. Etoposide could then be marketed in 175 mg vials to simplify preparation and administration.

Will it be possible to change clinical practice? Because current practice is not based on science, but rather myth handed down through the generations, it will not be easy. Remember, our ancestors used to think the world was flat. However, eventually science should win, because carefully conducted clinical trials clearly can change practice, including even such ingrained habits as BSA-based dosing.

Mark J. Ratain
University of Chicago
Chicago, IL

REFERENCES

1. du Bois D, du Bois EF: A formula to estimate the approximate surface area if height and weight be known. Arch Intern Med 17:863-871, 1916

2. Gehan EA, George SL: Estimation of human body surface area from height and weight. Cancer Chemother Rep 54:225-235, 1970

3. Freireich EJ, Gehan EA, Rall DP, et al: Quantitative comparison of toxicity of anticancer agents in mouse, rat, hamster, dog, monkey, and man. Cancer Chemother Rep 50:219-231, 1966

4. Morgan DJ, Bray KM: Lean body mass as a predictor of drug dosage. Implications for drug therapy. Clin Pharmacokinet 26:292-307, 1994

5. Efthymiopoulos C, Bramer SL, Maroli A: Effect of age and gender on the pharmacokinetics of grepafloxacin. Clin Pharmacokinet 33:9-17, 1997 (suppl 1)

6. Wing YK, Chan E, Chan K, et al: Lithium pharmacokinetics in Chinese manic-depressive patients. J Clin Psychopharmacol 17:179-184, 1997

7. Minto CF, Schnider TW, Egan TD, et al: Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development. Anesthesiology 86:10-23, 1997

8. Gurney HP, Ackland S, Gebski V, et al: Factors affecting epirubicin pharmacokinetics and toxicity: Evidence against using body-surface area for dose calculation. J Clin Oncol 16:2299-2304, 1998

9. Cosolo WC, Morgan DJ, Seeman E, et al: Lean body mass, body surface area and epirubicin kinetics. Anticancer Drugs 5:293-297, 1994

10. Gurney HP: Dose calculation of anticancer drugs: A review of the current practice and introduction of an alternative. J Clin Oncol 14:2590-2611, 1996

11. Grochow LB, Baraldi C, Noe D: Is dose normalization to weight or body surface area useful in adults [letter]? J Natl Cancer Inst 82:323-325, 1990

12. Reilly JJ, Workman P: Normalisation of anti-cancer drug dosage using body weight and surface area: Is it worthwhile? A review of theoretical and practical considerations. Cancer Chemother Pharmacol 32:411-418, 1993

13. Baker LH, Hirth JS, Carson E, et al: Cytochrome P4503A activity as a predictor of docetaxel toxicity and response. Proc Am Soc Clin Oncol 17:186a, 1998 (abstr 718)

14. Boddy AV, Ratain MJ: Pharmacogenetics in cancer etiology and chemotherapy. Clin Cancer Res 3:1025-1030, 1997

15. Fulcher GR, Farrer M, Walker M, et al: A comparison of measurements of lean body mass derived by bioelectrical impedance, skinfold thickness and total body potassium. A study in obese and non-obese normal subjects. Scand J Clin Lab Invest 51:245-253, 1991

16. de Fijter WM, de Fijter CW, Oe PL, et al: Assessment of total body water and lean body mass from anthropometry, Watson formula, creatinine kinetics, and body electrical impedance compared with antipyrine kinetics in peritoneal dialysis patients. Nephrol Dial Transplant 12:151-156, 1997

17. DeMario MD, Ratain MJ: Oral chemotherapy: Rationale and future directions. J Clin Oncol 16:2557-2567, 1998

18. Ratain MJ: Pharmacokinetics and pharmacodynamics, in DeVita VT, Hellman S, Rosenberg SA (eds): Principles and Practice of Oncology (ed 5). Philadelphia, PA, Lippincott-Raven, 1997, pp 375-385

X. Related Proceedings Appendix

There are no related proceedings.